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Ocular adverse events following intravitreal brolucizumab for neovascular age-related macular degeneration at a single tertiary care center

Huy V. Nguyen[1], **Angela S. Li**[1], **Amila R. Silva**[1], **Theodore Leng**[1]

[1]Byers Eye Institute at Stanford, Stanford University School of Medicine, Palo Alto, CA, USA

Abstract

Purpose: To determine the incidence of ocular adverse effects (AEs) following brolucizumab injection for neovascular age-related macular degeneration at a tertiary academic institution.

Design: Retrospective, single center cohort study.

Participants: All patients who received an intravitreal injection of brolucizumab 6 mg for neovascular age-related macular degeneration between October 7, 2019 and July 31, 2020.

Methods: Medical records of all patients who received brolucizumab 6 mg during the aforementioned time period were carefully reviewed and all ocular adverse effects after injection were charted.

Main Outcome Measures: Incidence of post-injection ocular AEs, including intraocular inflammation (IOI), and time to development of AEs after injection.

Results: A total of 77 patients received brolucizumab 6 mg for a total of 115 administrations during the study period. There were 4 AEs (3.5%), including three cases of IOI (2.6%), one central retinal artery occlusion, and one retinal detachment. Two men and two women were affected.

Conclusion: Ocular AEs, including those leading to severe vision loss, may develop after intravitreal brolucizumab 6 mg. A careful discussion of benefits and risks to brolucizumab should be conducted with all patients.

Precis: In this first case series of ocular adverse effects after brolucizumab 6 mg injection at a single tertiary care center, the incidence of ocular adverse effects was 3.5%, including a 2.6% incidence of intraocular inflammation.

Keywords

Age-related macular degeneration; retina – medical therapies; choroidal/retinal inflammation; anterior uveitis; arterial occlusive disease

Corresponding author: Theodore Leng, Byers Eye Institute at Stanford, 2452 Watson Court, Palo Alto, CA 94303, USA. tedleng@stanford.edu.

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Introduction

Intravitreal anti-vascular endothelial growth factor (aVEGF) therapy is the standard of care treatment for choroidal neovascularization (CNV) secondary to neovascular age-related macular degeneration (nAMD).[1,2] Ranibizumab and aflibercept have been approved by the Food and Drug Administration (FDA) for treatment of nAMD, and bevacizumab is widely used off-label. The newest commercially available aVEGF agent for intravitreal injection is brolucizumab, which was approved by the FDA on October 7, 2019. Brolucizumab is a humanized single-chain antibody fragment (scFv) that inhibits VEGF-A binding to VEGF receptors VEGFR1 and VEGFR2.[3] Due to its small size, brolucizumab is able to be delivered in a greater molar dose compared with larger molecules.[4] This allows for the possibility of better tissue penetration and increased duration of effect, which is desirable given the ongoing push towards decreasing treatment burden and frequent office visits for patients. In Phase III data from the HAWK and HARRIER trials, at 48 weeks of treatment for treatment-naïve nAMD, brolucizumab 6 mg/0.05 mL (dosed at either 8 or 12 weeks) demonstrated noninferior best-corrected visual acuity (BCVA) improvement and superior anatomic gains (in reducing retinal thickness and resolving retinal fluid) as compared with aflibercept 2 mg/0.05 mL (dosed at 8 weeks).[5,6]

As with any promising novel treatment, it is important to critically evaluate the ocular and systemic safety of brolucizumab. In HAWK and HARRIER at 48 weeks, there were several ocular adverse events (AEs) which were higher in the brolucizumab groups compared with aflibercept. Specifically, in HAWK, combined intraocular inflammation (IOI), defined as iritis and uveitis, was seen in 4.4% of brolucizumab 6 mg versus 0.3% in aflibercept 2 mg.[5] There was also several serious adverse effects in the brolucizumab group which were not reported in the aflibercept group, including retinal detachment, retinal artery occlusion, retinal artery thrombosis, and endophthalmitis.[5] When the results of HAWK and HARRIER were extended up to 96 weeks, these discrepancies were maintained. At 96 weeks, combined IOI occurred in 4.7% of patients in the brolucizumab 6 mg, compared with 0.6% of aflibercept 2 mg.[6] Several other discrepancies in AEs were revealed, including retinal pigment epithelial tear (3.3% in brolucizumab 6 mg versus 1.1% in aflibercept) and endophthalmitis (0.8% in brolucizumab 3 mg and 6 mg versus 0% in aflibercept). In HAWK, AEs related to ocular arterial thromboembolic events (ATEs) occurred in 1.1% of brolucizumab 3 mg, 1.4% in brolucizumab 6 mg, compared with 0.3% in aflibercept. In HARRIER, ATEs occurred in 1.6% of brolucizumab 6 mg compared with 0.5% in aflibercept. One post hoc analysis of a subset of HAWK/HARRIER data, performed by an independent safety review committee with Novartis, found that of 1088 brolucizumab treated eyes, 4.6% had definite or probably IOI, 3.3% had IOI with retinal vasculitis, and 2.1% had IOI with occlusive retinal vasculitis.[7,8]

At the time of this report, brolucizumab has been approved by the FDA for 20 months. In this time, other case reports and case series have emerged detailing serious ocular AEs – including IOI and occlusive RV --after administration of brolucizumab for nAMD.[9–13] For instance, a recent case series of retinal vasculitis after brolucizumab as reported to the American Society of Retina Specialists (ASRS) showed occlusive retinal vasculitis seen in 26 eyes of 25 patients, of which 12 eyes (46%) had a final visual acuity of 20/200 or

worse.[14] A recent Japanese case series discussed 3 patients who developed IOI and RV 11–18 days after receiving brolucizumab injections. They were subsequently treated with 30 mg/day of oral prednisone, a subtenon's triamcinolone injection, and topical betamethasone drops.[15,16]

The frequency of administration also appears to be related to the incidence of adverse events. The Phase 3 MERLIN study comparing brolucizumab 6 mg and aflibercept 2 mg every 4 weeks for patients wth nAMD showed a significantly higher rate of IOI (including RV and RO) for patients receiving brolucizumab compared to aflibercept. The trial was terminated early and all subsequent trial protocols were discontinued from 4-week dosing intervals after the loading phase.[17] In addition, brolucizumab-associated RV appears to have a strong female predominance (88–100%) and underlying cardiovascular disease may also be a risk factor.[10,14] However, no other patterns of medical, ocular, or allergic history has been linked to adverse events.[9]

In the current report, we describe the first case series of ocular adverse effects from intravitreal brolucizumab from a single tertiary academic center over the first 9 months after FDA approval, from October 7, 2019 to July 31, 2020. Over this time period at the Byers Eye Institute at Stanford, 77 patients received brolucizumab for a total of 115 administrations, and there were 4 adverse events that occurred.

The patients presented in the following case series all provided verbal informed consent for inclusion in the present study.

Case series

Case 1

A 95-year-old Caucasian female with bilateral nAMD experienced painless, unilateral vision loss in her right eye (OD) 4 weeks after her third injection of brolucizumab given every 6 weeks in that eye. Prior to her brolucizumab injections, she had received 43 monthly administrations of aflibercept in that eye for nAMD without any adverse effects. The switch to brolucizumab was due to persistence of subretinal fluid. On exam, her BCVA was counting fingers (CF) at 2 feet compared to 20/80 at the prior visit. A dilated fundus exam (DFE) during that visit showed arteriolar narrowing and vascular attenuation OD. She denied any recent weight loss, jaw claudication, malaise, or fever, and her CRP and ESR were normal. After consultation with neuroophthalmology, giant cell arteritis was deemed unlikely, so she was diagnosed with a central retinal artery occlusion (CRAO). The patient was offered a fluorescein angiogram, as well as presentation to the main hospital for a full cardiac and carotid workup, but she declined. The left eye (OS) received brolucizumab once but was switched back to aflibercept after the adverse event. After the CRAO, intravitreal injections were stopped OD due to limited visual prognosis.

Case 2

A 64-year-old Caucasian male with bilateral nAMD developed acute anterior uveitis and retinal vasculitis in his right eye 5 months after receiving brolucizumab injections OU. Prior to brolucizumab, he had previously been receiving aflibercept OU every 6 weeks for 3

years (24 doses), with no adverse effects. Upon the switch, he received two brolucizumab injections OD, 6 weeks apart, and one brolucizumab injection OS. Due to persistent subretinal fluid, he was switched back to aflibercept OU every 6 weeks for 3 injections. Two days after his most recent aflibercept injection, and 5 months after his last brolucizumab injection OD, he developed severe pain in that eye. On examination, he had conjunctival injection and 2+ cell in the anterior chamber without flare, keratic precipitates, or hypopyon. He was diagnosed with acute anterior uveitis and started on hourly topical prednisolone and cyclopentolate three times a day. The patient returned to clinic the following day complaining of worsening vision, and his BCVA had dropped to CF compared to 20/150 the day prior. He had increasing anterior chamber cell and flare, vitreous haze, and diffuse retinal vasculitis on exam and imaging. PCR analysis of anterior chamber paracentesis fluid was negative for VZV, HSV, CMV, and toxoplasmosis. Cultures were negative for bacteria and fungus. Other causes of uveitis were ruled out with a negative QuantiFERON, ANA, ANCA, ACE, CRP, ESR, syphilis treponemal screen, and rheumatoid factor. The patient was started on oral prednisone, 40 mg daily with a rapid taper to 20 mg. After one week, his vision OD improved to 20/200 and he had decreased leakage on fluorescein angiogram.

Case 3

An 80-year-old Asian female with bilateral nAMD treated with monthly aflibercept for 7 years developed blurry vision, pain, and redness OS 5 days after receiving her first injection of brolucizumab in that eye. On exam, her BCVA was at her baseline of 20/40. Due to the presence of anterior chamber cell OS, she was diagnosed with acute iritis OS. She was started on topical prednisolone 4 times a day and cyclopentolate 2 times a day OS and the iritis resolved after two weeks. The patient then switched back to aflibercept injections OU every 5 weeks. Two months later, and two weeks after an aflibercept injection, the patient once again developed acute iritis OS with keratic precipitates (KPs), without evidence of vitritis. A laboratory workup with ESR, CRP, RPR, CMP, CBC, ANCA, rheumatoid factor, lysozyme, HLA-B27 and QuantiFERON were all negative, although the patient had a positive ANA with a 1:80 titer. She was treated with valacyclovir 1 g and cyclopentolate three times a day in addition to hourly topical prednisolone, with resolution of inflammation after 1 week. Her eye remains quiescent.

Case 4

A 73-year-old Caucasian male with nAMD OD treated with aflibercept every 6 weeks for 9 months was switched to brolucizumab due to persistent subretinal fluid. At his follow-up appointment 6 weeks later, he complained of persistent blurry vision over the previous week. On exam, his BCVA was 20/70 (decreased from his baseline of 20/40) and he had inferior granulomatous KP and trace cell in the anterior chamber and vitreous. He was diagnosed with iritis OD and started on topical prednisolone for one week. The inflammation slowly resolved over the next month and his vision returned to baseline. He has since been receiving monthly intravitreal aflibercept in his right eye.

Discussion

The present report represents the first published case series of ocular adverse effects from intravitreal injection of brolucizumab at a single tertiary center. Over the 9 months since its FDA approval, intravitreal brolucizumab 6 mg was administered 115 times in the eyes of 77 patients at the Byers Eye Institute at Stanford. The total prevalence of ocular AEs was 4/115, or 3.5%. After an AE was recorded, no additional brolucizumab was administered for that patient, and patients were often switched back to intravitreal aflibercept. There was 1 case of CRAO (0.9%), 1 case of panuveitis with retinal vasculitis (0.9%), and 2 cases of anterior uveitis (1.7%). The total percentage of administrations resulting in combined IOI was 2.6%. While the sample size is small, these rates are comparable to those reported with broluzicumab 6 mg in the HAWK trial, which reported retinal detachment in 0.3% and uveitis in 2.2% at 48 weeks, and IOI in 4.4% at 96 weeks.

While rare, these ocular adverse effects can have consequential visual loss. In Case 1, the patient's retinal artery occlusion dropped her vision from 20/80 to counting fingers, a loss of approximately 40 ETDRS letters. Since the patient wished not to have a fluorescein angiogram, it is possible that she could have had an undiagnosed retinal vasculitis from brolucizumab leading to her retinal artery occlusion. In Case 2, the patient developed noninfectious retinal vasculitis with associated vision loss. Despite his most recent injection being aflibercept, he had had 24 doses of aflibercept over the preceding 3 years without any adverse effects, so it was thought that the switch to brolucizumab had either directly or indirectly caused the inflammation. This recurrence of IOI after switching back to aflibercept from brolucizumab was also seen in Case 3, which raises the possibility that brolucizumab can have a sensitization mechanism to other anti-VEGF agents in the development of IOI. From HAWK and HARRIER, 4 of 730 patients (0.5%) treated with brolucizumab 6 mg experienced IOI and retinal artery occlusion with loss of 15 ETDRS letters or more. This complication has not been reported with the other FDA-approved aVEGF agents.[2,18] In fact, brolucizumab is the first FDA-approved aVEGF agent associated with noninfectious retinal vasculitis.[5,9–11]

This study also demonstrates the variability of time to ocular adverse effects after brolucizumab administration. Within these four cases, adverse effects occurred as early as 5 days and as late as 20 weeks after last brolucizumab injection, with an average of 56 days after the antecedent injection. Others have reported an average of 29 days to IOI (Baumal et al. in their series of 15 eyes[10]) and 25 days to IOI (from the 26 cases reported to the American Society of Retinal Specialists (ASRS) and analyzed by the ASRS Research and Safety in Therapeutics Committee[14]). Around half (48%) of IOI occurred within the first 3 months of brolucizumab therapy, and 74% occurred within the first 6 months.[19] However, in the ASRS Research and Safety in Therapeutics Committee Report in Spring 2020, the upper range of presentation of IOI from the first brolucizumab injection was 146 days.[14] Since the HAWK and HARRIER studies only reported the cumulative incidence of AEs at the end of the study period (48 or 96 weeks),[5,6] it is important for providers choosing brolucizumab to have a guideline on when to expect most cases of brolucizumab-associated AEs to declare themselves.

While the reason is currently unknown, brolucizumab-associated IOI occurs at a higher rate compared to other anti-VEGF agents despite the fact that it lacks the Fc region and cannot activate the complement pathway or participate in antibody-mediated cytotoxicity.[19] First, the antibody fragment for brolucizumab is of a smaller molecular weight than other aVEGF agents, leading to a higher concentration of drug in the same volume and possibly increased binding of VEGF. A type IV hypersensitivity reaction has been proposed, where vascular occlusion can result from an intravascular inflammatory response which develops along the vessel wall where plasma is in contact with the foreign drug.[11] The idea of delayed hypersensitivity is supported by vitreous sample analysis in a recent clinicopathologic case report of a 76-year-old woman who developed posterior uveitis and retinal vasculitis after her third injection of brolucizumab.[20]

Like the case of retinal vasculitis presented by Jain et al.[11] our case of retinal vasculitis occurred after multiple injections of brolucizumab, so it is not possible to guarantee safety to the medication after the patient has successfully tolerated it once. Another possible explanation for the vasculitis seen after brolucizumab is that a type III hypersensitivity reaction to the antibody fragment causes aggregates of IgG/IgM complexes to deposit in retinal vessels.[21] Finally, it has been suggested that the higher prevalence of anti-drug antibodies (ADA) to brolucizumab, cited at 36% to 52% of treatment naïve patients, compared to 0% to 3% for ranibizumab and aflibercept, could explain the higher rates of IOI after brolucizumab injection[19,22]

The debate continues on which aVEGF medication is most effective for patients with active nAMD. In August 2018, based on the second-year data from the Phase 3 VIEW 1 and 2 trials, aflibercept secured FDA approval for dosing every 12 weeks (q12w) for nAMD. Brolucizumab, likewise, was approved for dosing of up to q12w. However, in HAWK and HARRIER, fewer than 56% of patients in the brolucizumab 6-mg group had maintained q12w dosing at the end of the initial 48-week period, with the percentage dropping to fewer than 45% at 96 weeks.[5,6] If a large percentage of patients on brolucizumab would need to convert to q8w dosing, the predicted decrease in treatment burden and patient travel of brolucizumab treatment would be lost. Given the risks of intravitreal brolucizumab, the clinician must carefully weigh the benefits of a potentially longer treatment interval and sustained anatomic improvement against the possibility of vision loss from a serious ocular adverse event. Brolucizumab is clinically noninferior to current standard of care for nAMD, but it is also associated with a novel uncommon sight-threatening adverse event in occlusive retinal vasculitis.

There are several limitations to this study. First, the study sample size is small. The patients in Cases 1 and 2 also received multiple injections of brolucizumab 6 weeks apart, which is a smaller interval than the 8-week intervals in the HAWK and HARRIER study. This may suggest that intravitreal brolucizumab should not be dosed in shorter than 8-week intervals. And while this study certainly suggests an association between brolucizumab and IOI, it cannot prove causation, as intraocular inflammation can also result from a variety of additional factors, such as infection, autoimmune causes, toxicity, and malignancy. Finally, none of the patients in this series were treatment naïve, and the decision to switch to brolucizumab from another anti-VEGF agent was made by individual providers.

Subsequent studies are required to elucidate whether there exist qualifiers for patients which will place them at higher risk for adverse events after treatment with intravitreal brolucizumab. Additional research is also required to show if eyes treated with intravitreal brolucizumab are at risk for additional adverse effects when switched back to a different intravitreal anti-VEGF medication.

Conclusion

Ocular adverse events, including those leading to severe vision loss, are reported after intravitreal brolucizumab 6 mg. As the first case series from a single institution, this study validates the published rates of IOI after brolucizumab in HAWK and HARRIER.

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